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of down-regulated control mechanisms. ANGPT2, both as circulating factor and at the lung level, represents a much more direct indicator for the pathogenic mechanism underlying COVID-19 acute respiratory distress syndrome and therefore is, in our view, a more powerful candidate prognostic factor. Not less important, two tests 3 days apart may be simpler and more affordable than the complex low vascular signature proposed.

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Authors' Reply

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From the Division of Pulmonary and Critical Care Medicine, Department of Medicine, New York-Presbyterian Hospital−Weill Cornell Medical Center, Weill Cornell Medicine, New York; the Department of Medicine,† New York-Presbyterian Hospital−Weill Cornell Medical Center, New York; and the Institute of Computational Biomedicine‡ and Department of Physiology and Biophysics,§ Weill Cornell Medicine, New York, New York

We thank Melegari et al for their letter and their interest in our article. Our study derived a 22-protein vascular injury signature based on blood proteins' association with both mortality and platelet level and showed that this signature correlated with clinical (eg, mortality and recovery) as well as pathophysiological [eg, platelets, angiopoietin 2 (ANGPT2), and necrotic vascular cell death] readouts throughout the time course of coronavirus disease 2019 (COVID-19) acute respiratory distress syndrome (ARDS).[1] Notably, the data demonstrated that this association held even when non−COVID-19 ARDS subjects were included in the analysis.

Melegari et al suggest that serial measurements of ANGPT2 separated by 3 days are a more feasible prognostic biomarker for COVID-19 than the baseline measurement of the 22-protein signature derived in the mentioned article.[1] After a multivariable adjustment, a twofold increase in ANGPT2 over 3 days accurately predicted mortality in a mixed disease severity cohort of COVID-19 subjects.[2] These findings fit nicely with the robust literature linking ANGPT2 and prognosis in sepsis/acute lung injury: ANGPT2 has been linked to prognosis in sepsis[3,4] and ARDS,[5] including a large meta-analysis.[6] Serial ANGPT2 measurements have similarly been linked to ARDS prognosis in non−COVID-19 infection−related acute lung injury,[7] further supporting ANGPT2 as a robust prognostic biomarker. Although the reported protein signature is in part defined by its association with patient mortality, it was not primarily intended for clinical prognosis applications.

Instead, these findings better fit within a growing body of evidence linking the Tie2/angiopoietin axis with platelet activation in systemic inflammation and acute lung injury. Disruption of the endothelial Tie2 axis has been shown to be a sentinel event in septic disseminated intravascular coagulation, with loss of Tie2 signaling preceding signs of overt platelet consumption and Tie2 activation working to normalize prothrombotic responses.[8] More recently, alterations in the Tie2/angiopoietin axis have been linked to the procoagulant endothelial dysfunction in severe COVID-19.[9] Our article offers a relevant complement to these findings in several ways. First, it links the dysregulated Tie2/angiopoietin axis to platelet level and blood markers of coagulopathy in a diverse ARDS cohort (COVID-19 as well as bacterial and influenza ARDS), demonstrating the clinical relevance of aberrant vascular activation and coagulopathy to a general ARDS population. And second, by including ARDS subjects with diverse etiologies of low platelet levels (eg, lack of platelet production in patients with malignancy), the link between the Tie2/angiopoietin axis and platelet level can be generalized to non−platelet-consumptive ARDS processes. As platelets are essential sources of angiocrine factors, including the endothelial-stabilizing angiopoietin-1 and angiogenic factors platelet-derived growth factor-A and platelet-derived growth factor-B, deficiency in these factors may reflect an inherent vascular

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vulnerability in these malignancy patients with low platelets who develop ARDS.[10]

Although the study was not a prognostic biomarker study, it may still inform patient selection for future vascular targeted therapies in ARDS. Previous vascular targeted trials in ARDS have failed,[11–13] likely due to inclusion of ARDS subjects with minimal vascular injury. Conversely, our vascular injury signature demonstrates that in select ARDS subjects, low expression of important vascular proteins is linked to increased blood and lung microvascular ANGPT2 expression as well as platelet-rich microthrombi and induction of necrotic vascular cell death. More important, these ARDS subjects with high vascular injury are readily identifiable by their baseline platelet counts, which are routinely measured in clinical practice and may offer a simple strategy for patient enrollment in clinical trials. However, further studies are necessary to identify an optimal cutoff for patient stratification in this context.

In conclusion, both types of investigation discussed herein are essential to improve understanding of vascular injury in acute lung injury: Melegari et al have added to the rich literature identifying ANGPT2 as a powerful ARDS prognostic biomarker; whereas, our study contributed to the molecular characterization of the vascular injury heterogeneity in ARDS and might help future scientists better identify high vascular injury subjects for targeted therapies.

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